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(71) Applicant *(for all designated States except MG US)*: ASTRA PHARMACEUTICALS LTD. [GB/GB]; Home Park, Kings Langley, Herts WD4 8DH (GB).

(71) Applicant *(for MG only)*: ASTRA AKTIEBOLAG [SE/SE]; S–151 85 Södertälje (SE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: DIXON, John [GB/GB]; Astra Charnwood, Bakewell Road, Loughborough, Leics. LE11 5RH (GB). INCE, Francis [GB/GB]; Astra Charnwood, Bakewell Road, Loughborough, Leics. LE11 5RH (GB).

(74) Agent: ASTRA AKTIEBOLAG; Intellectual Property, Patents, S–151 85 Södertälje (SE).

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(54) Title: PHARMACEUTICAL COMPOSITIONS COMPRISING A COMPOUND HAVING DOPAMINE (D_2) RECEPTOR AGONIST ACTIVITY AND A COMPOUND (B) HAVING β_2–ADRENORECEPTOR AGONIST ACTIVITY

(57) Abstract

The present invention provides pharmaceutical compositions comprising a compound (A) having dopamine (D_2) receptor agonist activity and a compound (B) having β_2–adrenoreceptor agonist activity. Preferably the composition comprises, as compound (A), cabergoline or ropinirole and as compound (B), formoterol, [R,R]–formoterol, salmeterol, [R]–salmeterol, [R]–salbutamol or terbutatine. The composition is used in the treatment of reversible obstructive airways diseases.

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PHARMACEUTICAL COMPOSITIONS COMPRISING A COMPOUND HAVING DOPAMINE (D_2) RECEPTOR AGONIST ACTIVITY AND A COMPOUND (B) HAVING β_2-ADRENORECEPTOR AGONIST ACTIVITY

The present invention relates to pharmaceutical compositions and their use in the treatment of reversible obstructive airways diseases.

In accordance with the present invention, there is provided a pharmaceutical composition comprising a compound (A) having dopamine (D_2) receptor agonist activity and a compound (B) having β_2-adrenoreceptor agonist activity, wherein the compounds (A) and (B) are different.

In particular, the present invention provides a pharmaceutical composition comprising a compound (A) having dopamine (D_2) receptor agonist selected from the group consisting of:

Apomorphine ((R)-5,6,6a,7-tetrahydro-6-methyl-4H-dibenzo[de,g]quinoline-10,11-diol),
Bromocriptine ((5'α)-2-bromo-12'-hydroxy-2'-(1-methylethyl)-5'-(2-methylpropyl) ergotaman-3',6',18-trione),
Cabergoline ((8β)-N-[3-(dimethylamino)propyl]-N-[(ethylamino)carbonyl]-6-(2-propenyl)ergoline-8-carboxamide),
Lisuride (N'-[(8α)-9,10-didehydro-6-methylergolin-8-yl]-N,N-diethylurea),
Pergolide ((8β)-8-[(methylthio)methyl]-6-propylergoline),
Levodopa (3-hydroxy-L-tyrosine),
Pramipexole ((S)-4,5,6,7-tetrahydro-N^6-propyl-2,6-benzothiazolediamine),
Quinpirole hydrochloride (trans-(-)-4aR-4,4a,5,6,7,8,8a,9-octahydro-5-propyl-1H-pyrazolo[3,4-g]quinoline hydrochloride),
Ropinirole (4-[2-(dipropylamino)ethyl]-1,3-dihydro-2H-indol-2-one) and
Talipexole (5,6,7,8-tetrahydro-6-(2-propenyl)-4H-thiazolo[4,5-d]azepin-2-amine)

and

a compound (B) having β_2-adrenoreceptor agonist activity selected from the

group consisting of:

Clenbuterol (4-amino-3,5-dichloro-α-[[(1,1-dimethylethyl)amino]methyl]-benzenemethanol),

Fenoterol (5-[1-hydroxy-2-[[2-(4-hydroxyphenyl)-1-methylethyl]amino]ethyl]-1,3-benzenediol),

Formoterol ((±)-N-[2-hydroxy-5-[1-hydroxy-2-[[2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenylformamide),

[R,R]-Formoterol,

Hexoprenaline (4,4'-[1,6-hexanediylbis[imino(1-hydroxy-2,1-ethanediyl)]]bis-1,2-benzenediol),

Isoetharine (4-[1-hydroxy-2-[(1-methylethyl)amino]butyl]-1,2-benzenediol),

Isoprenaline (4-[1-hydroxy-2-[(1-methylethyl)amino]ethyl]-1,2-benzenediol),

Metaproterenol (5-[1-hydroxy-2-[(1-methylethyl)amino]ethyl]-1,3-benzenediol),

Picumeterol (4-amino-3,5-dichloro-α-[[[6-[2-(2-pyridinyl)ethoxy]hexyl]amino]-methyl]benzenemethanol),

Pirbuterol (α^6-[[(1,1-dimethylethyl)amino]methyl]-3-hydroxy-2,6-pyridinedimethanol),

Procaterol ((R*, S*)-(±)-8-hydroxy-5-[1-hydroxy-2-[(1-methylethyl)amino]butyl]-2(1H)-quinolinone),

Reproterol (7-[3-[[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino]propyl]-3,7-dihydro-1,3-dimethyl-1H-purine-2,6-dione),

Rimiterol (4-(hydroxy-2-piperidinylmethyl)-1,2-benzenediol),

Salbutamol ((±)-α^1-[[(1,1-dimethylethyl)amino]methyl]-4-hydroxy-1,3-benzenedimethanol),

[R]-Salbutamol,

Salmeterol ((±)-4-hydroxy-α^1-[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol),

[R]-Salmeterol,

Terbutaline (5-[2-[(1,1-dimethylethyl)amino]-1-hydroxyethyl]-1,3-benzenediol),

Tulobuterol (2-chloro-α-[[(1,1-dimethylethyl)-amino]methyl]benzenemethanol) and

TA-2005 (8-hydroxy-5-[(1R)-1-hydroxy-2-[N-[(1R)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]carbostyril hydrochloride).

The compounds (A) and (B) above are known to be used separately as pharmaceuticals but the use of a compound (A) in combination with a compound (B) in a pharmaceutical composition is not known.

Certain compounds (A) and (B) are capable of existing in stereoisomeric forms. Unless otherwise indicated, it should be understood that the invention encompasses the use of all geometric and optical isomers of compounds (A) or of compounds (B), and mixtures thereof including racemates. The use of tautomers and mixtures thereof also form an aspect of the present invention.

Preferably the composition comprises, as compound (A), cabergoline or ropinirole.

The composition preferably comprises, as compound (B), formoterol, [R,R]-formoterol, salmeterol, [R-]-salmeterol, [R]-salbutamol or terbutaline.

The pharmaceutical composition of the invention may be prepared by mixing a compound (A) with a compound (B). Therefore, in another aspect of the present invention, there is provided a process for the preparation of a pharmaceutical composition which comprises mixing a compound (A) with a compound (B) as hereinbefore defined. The pharmaceutical composition of the invention may, and indeed will usually, contain various other ingredients known in the art, for example, a carrier, binder, lubricant, diluent, stabilising agent, buffering agent, emulsifying agent, viscosity-regulating agent, surfactant, preservative, flavouring or colorant. Thus the pharmaceutical composition of the invention will typically comprise a total amount of compound (A) and compound (B) (the active ingredients) in the range from 0.05 to 99 %w (per cent by weight), more preferably in the range from 0.10 to 70 %w, all percentages by weight being based on total composition.

The pharmaceutical compositions of the present invention have both β_2-adrenoreceptor agonist activity and dopamine (D_2) receptor agonist activity. β_2-Adrenoreceptor agonist activity may be determined in a test carried out on the isolated trachea of the guinea pig according to the method of I.G. Dougall *et al.*, Br. J. Pharmacol., 1991, 104, 1057. Dopamine (D_2) receptor agonist activity may be assessed by the binding affinities of compounds for the dopamine receptor binding sites in bovine pituitary membranes according to the method of D.R. Sibley *et al.*, J. Biol. Chem., 1982, 257(11), 6351-6361, or, in the functional rabbit isolated ear artery screen described by R. Brown *et al.*, Br. J. Pharmacol., 1981, 73, 189P.

The present pharmaceutical compositions are particularly suitable for use in the treatment of reversible obstructive airways diseases such as asthma (including bronchial asthma, allergic asthma and intrinsic asthma, e.g. late asthma and airway hyper-responsiveness), chronic bronchitis and other chronic obstructive pulmonary diseases.

Thus, the present invention further provides a pharmaceutical composition as hereinbefore defined for use in therapy.

In a further aspect, there is provided the use of a pharmaceutical composition as hereinbefore defined in the manufacture of a medicament for the treatment of reversible obstructive airways disease, in particular for the treatment of asthma or chronic bronchitis.

The present invention still further provides a method of treating, or reducing the risk of, a reversible obstructive airways disease in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a therapeutically effective amount of a pharmaceutical composition as hereinbefore defined.

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compounds (A) and (B) employed, the mode of administration, the treatment desired and the disorder indicated. However, in general, satisfactory results will be

obtained when the pharmaceutical composition is administered such that the total daily dosage of compound (A) and compound (B) together is in the range from 5 to 1500 μg, e.g. from 10 to 1450 μg or from 20 to 1400 μg.

The pharmaceutical composition of the invention may be administered topically (to the lung and/or airways) in the form of solutions, suspensions, aerosols and dry powder formulations; or systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders or granules, or by parenteral administration in the form of solutions or suspensions.

For example metered dose inhaler devices may be used to administer the active ingredients, dispersed in a suitable propellant and with or without additional excipients such as ethanol, surfactants, lubricants or stabilising agents.

Suitable propellants include hydrocarbon, chlorofluorocarbon and hydrofluoroalkane (e.g. heptafluoroalkane) propellants, or mixtures of any such propellants. Especially preferred propellants are P134a and P227, each of which may be used alone or in combination with other propellants and/or surfactants and/or other excipients.

Nebulised aqueous suspensions or, preferably, solutions may also be employed, with or without a suitable pH and/or tonicity adjustment, either as a unit-dose or multi-dose formulations.

Dry powder inhalers may be used to administer the active ingredients, alone or in combination with a pharmaceutically-acceptable carrier, in the latter case either as a finely divided powder or as an ordered mixture. The dry powder inhaler may be single dose or multi-dose and may utilise a dry powder or a powder-containing capsule.

Metered dose inhaler, nebuliser and dry powder inhaler devices are well known and a variety of such devices are available.

Tablets and gelatin capsules, which may be coated if desired, containing the active ingredients may, for example, also include one or more diluents, carriers, binders, lubricants or stabilising agents.

Injectable solutions of the active ingredients may also contain, for example, one or more preservatives, stabilising agents, viscosity-regulating agents, emulsifying agents or buffering agents.

CLAIMS

1. A pharmaceutical composition comprising a compound (A) having dopamine (D_2) receptor agonist activity and a compound (B) having β_2-adrenoreceptor agonist activity, wherein the compounds (A) and (B) are different.

2. A composition according to Claim 1 comprising a compound (A) having dopamine (D_2) receptor agonist activity selected from the group consisting of apomorphine, bromocriptine, cabergoline, lisuride, pergolide, levodopa, pramipexole, quinpirole hydrochloride, ropinirole and talipexole, and a compound (B) having β_2-adrenoreceptor agonist activity selected from the group consisting of clenbuterol, fenoterol, formoterol, [R,R]-formoterol, hexoprenaline, isoetharine, isoprenaline, metaproterenol, picumeterol, pirbuterol, procaterol, reproterol, rimiterol, salbutamol, [R]-salbutamol, salmeterol, [R]-salmeterol, terbutaline, tulobuterol and TA-2005.

3. A composition according to Claim 2, wherein, as compound (A), cabergoline or ropinirole is used.

4. A composition according to Claim 2, wherein, as compound (B), formoterol, [R,R]-formoterol, salmeterol, [R-]-salmeterol, [R]-salbutamol or terbutaline is used.

5. A pharmaceutical composition as claimed in any one of Claims 1 to 4 for use in therapy.

6. Use of a pharmaceutical composition as claimed in any one of Claims 1 to 4 in the manufacture of a medicament for the treatment of reversible obstructive airways disease.

7. A method of treating, or reducing the risk of, a reversible obstructive airways disease in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a therapeutically effective amount of a pharmaceutical composition as defined in any one of Claims 1 to 4.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 98/02427

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 45/06, A61K 31/435, A61K 31/40, A61K 31/135
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4590206 A (RAYMOND B. FORRESTER ET AL), 20 May 1986 (20.05.86), column 4, lines 42-57	1-7
Y	US 5551489 A (EVA A. C. TROFAST ET AL), 3 Sept 1996 (03.09.96), claims	1-7
Y	US 5288498 A (THEODORE H. STANLEY ET AL), 22 February 1994 (22.02.94), claims 1, 39, 67, 73, 77	1-7

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
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Date of the actual completion of the international search	Date of mailing of the international search report
21 April 1999	29 -04- 1999
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Anneli Jönsson Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 98/02427

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Thorax, Volume 34, 1979, K M Christensen et al, "A double-blind trial of bromocriptine in steroid dependent asthma", page 284 - page 285, page 284, column 1, lines 1-9; column 1, line 41 - column 2, line 4; column 2, line 9 - line 10 -- --------	1-7

INTERNATIONAL SEARCH REPORT

International application No.
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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 7
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Claim 7 is directed to method of treatment of the human or animal body by therapy methods practised on the human or animal body/Rule 39.1(iv). Nevertheless, a search has been executed for this claims. The search has been based on the alleged effects of the composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

02/03/99

International application No.
PCT/SE 98/02427

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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INTERNATIONAL SEARCH REPORT

Information on patent family members

02/03/99

International application No.
PCT/SE 98/02427

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